PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PA136265/PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IB2004/003855	International filing date *(day/month/year)* 24.11.2004	Priority date *(day/month/year)* 25.11.2003
International Patent Classification (IPC) or national classification and IPC C07F15/00, A61P35/00		
Applicant PLATCO TECHNOLOGIES (PROPRIETARY) LIMITED		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 9 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23.09.2005	22.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Richter, H Telephone No. +49 89 2399-8539

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/003855

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-3, 7, 8, 10, 12-20	as originally filed
4-6, 9, 11	received on 23.09.2005 with letter of 22.09.2005

Claims, Numbers

1-15, 16(part)	as originally filed
16(part), 17-53	received on 23.09.2005 with letter of 22.09.2005

Drawings, Sheets

1/5-5/5	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-38,40-53
	No:	Claims	39
Inventive step (IS)	Yes:	Claims	1-38,40-53
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-35, 37-53
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1
Quoted documents:

D1 : DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; UTTECHT, J.-G. ET AL: "Synthesis, vibrational spectra and normal coordinate analysis of (n-Bu4N)2[Pt(SCN)n(ox)], n = 2, 4, and crystal structure of [(C5H5N)2CH2][Pt(SCN)4(ox)]" XP002317073 retrieved from STN Database accession no. 2002:781520

D2 : US 6 376 057 B1 (AKAO MUTSUO ET AL) 23 April 2002 (2002-04-23)

D3 : DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SONG, RITA ET AL: "Synthesis and selective tumor targeting properties of water soluble porphyrin-Pt(II) conjugates. [Erratum to document cited in CA137:362598]" XP002317067 retrieved from STN Database accession no. 2002:854473

D4 : DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KHUZAIE, RULA F. ET AL: "Screening for anticomplementary activity of some platinum (II) and palladium (II) complexes with various donor ligands and anions" XP002317068 retrieved from STN Database accession no. 2002:445382

D5 : DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; RASHAN, LUAY J. ET AL: "In vitro antitumor activity of platinum (II) complexes with various nitrogen containing ligands" XP002317069 retrieved from STN Database accession no. 1998:522331

D6 : DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PRIGNANO, ANDREA L. ET AL: "Silica-anchored bis(trialkylphosphine)platinum oxalate: a photogenerated catalyst for olefin hydrosilation" XP002317070 retrieved from

STN Database accession no. 1987:77537

D7 : DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PUNIYANI, SUSHIL ET AL: "Platinum(II) complexes of cyclohexanone and cyclopentanone thiosemicarbazones" XP002317071 retrieved from STN Database accession no. 1985:447222

D8 : DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SYAMAL, A. ET AL: "Synthesis of new platinum(II) complexes with ethanethiolamine, o-aminothiophenol and bidentate carboxylic acids" XP002317072 retrieved from STN Database accession no. 1983:209058

D9 : US 5 281 447 A (BRADY ET AL) 25 January 1994 (1994-01-25)

D10 : EP 0 115 929 A (TANABE SEIYAKU CO., LTD) 15 August 1984 (1984-08-15)

D11 : DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MIZUNO, MASAGI: "Linear chain compound bisoxalatoplatinate complexes" XP002317074 retrieved from STN Database accession no. 1989:432596

D12: XP000953019 ISOTERISM AND MOLECULAR MODIFICATION IN DRUG DESIGN

2
INDEPENDENT CLAIM 23
D8 is considered to represent the most relevant state of the art with respect to claim 23. This document discloses 2-aminoethanethiol and 2-aminobenzenethiol complexes.

From this, the complex according to independent claim 23 differs in the feature "heterocyclic amine with thioetheral S".

2.1.
The subject-matter of claim 23 is therefore novel (Article 33(2) PCT) The problem to be solved by the present invention may be regarded as providing a new anti-cancer agent.

2.2.
The solution to this problem proposed in claim 23 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons:
Prior art anti-cancer complexes known from D5 do not show nor suggest the distinguishing feature mentioned under 2.

3
INDEPENDENT CLAIM 39

3.1
The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 39 is not new in the sense of Article 33(2) PCT. Document D3 discloses (CA registry numbers): RN 475285-35-9 and RN 121730-28-7.

3.2
The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 39 is not new in the sense of Article 33(2) PCT. Document D4 discloses (CA registry numbers): RN 121730-28-7, RN 222841-83-0. Therapeutic use is also described in D4.

3.3
The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 39 is not new in the sense of Article 33(2) PCT. Document D5 discloses (CA registry number): RN 213538-22-8. Anti-cancer activity is also described.

3.4
The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 39 is not new in the sense of Article 33(2) PCT. Document D6 discloses (CA registry number): RN 106633-65-2.

3.5

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 39 is not new in the sense of Article 33(2) PCT. Document D7 discloses (CA registry numbers): RN 97178-06-8; RN 97178-10-4.

3.6

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 39 is not new in the sense of Article 33(2) PCT. Document D8 discloses (CA registry numbers): RN 84840-228-8; RN 85744-21-4.

3.7

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 39 is not new in the sense of Article 33(2) PCT. Document D1 discloses (the references in parentheses applying to this document): RN 481038-76-0; RN 481038-82-8; RN 481038-80-6

3.8

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 39 is not new in the sense of Article 33(2) PCT. Document D9 discloses (the references in parentheses applying to this document) the following Pt-oxalate complexes:

Pt(C2 O4)(SEt2)2	(column 10, line 57)
Pt(C2 O4)(SEt2)[P(I-Pr)3]	(column 10, line 61)
Pt(C2 O4)(SEt2)[P(c-Hx)3]	(column 10, line 62)
Pt(C2 O4)(SEt2)(PEt3)	(column 10, line 65)
Pt(C2 O4)(SEt2)(PPh3	(column 10, line 66)

3.10.

Additional anticipations for claim 39 are: the not yet mentioned Pt complexes according to D9, column 10, line 52 to column 11, line 7; D2, column 8, lines 25 - 27 in connection with

column 7, lines 49 - 65; D10, examples 7 and 16; and D11.

4
INDEPENDENT CLAIM 1

4.1
US-A-4169846 quoted by the applicant himself in the application at page 2 and document D10 are both considered to represent the most relevant state of the art with respect to claim 1. D10 discloses (the references in parentheses applying to this document): a preparation process similar to the one described at page 2 of the application (pages 4-7).

From this, the process of independent claim 1 differs in that no Ag compound is used as reagent.

4.1.1
The subject-matter of claim 1 is therefore novel (Article 33(2) PCT) The problem to be solved by the present invention may be regarded as providing a silver free product.

4.1.2
The solution to this problem proposed in claim 1 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons:
Bis-dicarboxylatoplatinate (II) complexes known from D2 (column 8, line 25: bis (oxalato)platinum (II) acid); D10 (page 8, line 9); and D11 have not yet been suggested as a starting material for the preparation of dicarboxylatoplatinate (II) complexes according to claim 1.

4.1.3
Claims 2-22 are dependent on claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

5

INDEPENDENT CLAIMS 24-35

5.1
These claims are more specific than claim 23 and could be dependent therefrom. Hence, claims 24-34 are likewise novel and inventive. Claim 35 is even further away from the prior art than claims 23-34 and is likewise novel and inventive.

6
INDEPENDENT CLAIM 40

6.1
Document D8, which is considered to represent the most relevant state of the art, discloses (the references in parentheses applying to this document): a process for preparing a mono-dicarboxylatoplatinate (II) from a platinum (II)-complex K2[PtCl4] .

From this, the process of independent claim 40 differs in the higher amounts of dicarboxylate and the fact that the dicarboxylate is limited to oxalate.

6.2
The subject-matter of claim 40 is therefore novel and inventive (Article 33(2 and 3) PCT).

7
Document D11, which is probably closer than D8 refers to a parent document which is not in an official language of the EPO. This document cannot be considered in this written opinion.

8. Claim 37
Claim 37 is dependent on claims 23-35 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

9. Claims 36, 38
Claims 36 and 38 relate to the use of new and inventive compounds. Therefore, these claims are also acceptable with respect to PCT Guidelines 13.19

10.
Claim 36 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

For the assessment of the present claim 36 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment (claims 37 and 38).

Re Item VII
Certain defects in the international application

10.
Art. 5 PCT is not met by claims 23-26, 28-31 and 33-35

The applicant has quite convincingly shown that a skilled person was able to prepare some of the compounds of claim 23 in analogy to the compounds of claims 27 and 32 (examples 6 - 8 in the description) at the time of the priority of the present application or earlier. However, the applicant failed to provide any evidence that the other claimed compound, namely those of claims 23 (partly) and claims 24-26, 28-31 and 33-35 have actually been prepared. In this context the pharmacological activity of such compounds for which protection is sought represents pure intellectual speculation thereby giving rise to the question as to whether the present application is in fact directed to a (technical) invention in the sense of the PCT, or rather to a mental act which
would be excluded from patent protection in the regional phase for instance under the EPC. The international examining authority would point to established jurisprudence of the Boards of Appeal, that inventions within the meaning of the EPC, on which patents are to

be granted, are required to make a contribution to the art, i.e. to provide a technical solution to problems arising in the art. Patents under the EPC are not designed for the purpose of reserving an unexplored field of research for a particular applicant, rather they are designed to protect the factual results of successful research as reward for making available concrete technical results to the public. As the applicant never had any of the claimed compounds according to claims 24-26, 28-31 and 33-35 in his hands, their alleged pharmaceutical activity is pure speculation and mere hope. In the absence of any corroborating evidence about a pharmaceutical activity of the virtual compounds of these claims an unverifiable statement in the application is not sufficient to make credible the purported pharmaceutical activity for substantially all compounds claimed by claim 23.

dissolving the product in distilled water and adding an oxalate such as $Cs_2C_2O_4$, which transforms the dicarboxylatoplatinate(II) species into a species that can be separated from the dissolved product by filtration.

The neutral bidentate ligand is typically an amine.

The amine may be a diamine.

Where the method is for the preparation of chemically and optically pure oxaliplatin, the ligand is optically pure trans-ℓ-1,2-diaminocyclohexane.

The neutral bidentate ligand may contain donor atoms other than N, or N together with a donor atom other than N, typically S and Se, for example:

- neutral bidentate heterocyclic amines with an S donor atom (for example thioethereal groups), such as:

1-alkyl/aryl-2-alkylthioalkyl/aryl heterocyclic amines, particularly imidazoles or pyridines, for example:

Ligand (i) 1-methyl-2-methylthioethylimidazole
Ligand (ii) 1-methyl-2-methylthiopropylimidazole
Ligand (iii) 1-butyl-2-methylthiomethylimidazole
Ligand (iv) 1-methyl-2-methylthiomethylimidazole
Ligand (v) 1-butyl-2-methylthioethylimidazole
Ligand (vi) 2-methylthiomethylpyridine
Ligand (vii) 2-methylthioethylpyridine
Ligand (viii) 2-methylthiopropylpyridine;

- aminoalkylthioalkyl/aryl compounds for example:

Ligand (ix) 1-amino-2-thiomethylethane
Ligand (x) 1-amino-2-thioethylethane;

- dithioethers for example:

Ligand (xi) 2,5-dithiahexane;

- diseleno ethers for example:

Ligand (xii) 2,5-diseleno hexane; etc.

New oxalatoplatinum(II) complexes containing S or Se donor atoms that can be prepared using the method of the invention include:

Complex (i) oxalato(1-methyl-2-methylthioethylimidazole)platinum(II)
Complex (ii) oxalato(1-methyl-2-methylthiopropylimidazole)platinum(II)
Complex (iii) oxalato(1-butyl-2-methylthiomethylimidazole)platinum(II)
Complex (iv) oxalato(1-methyl-2-methylthiomethylimidazole)platinum(II)
Complex (v) oxalato(1-butyl-2-methylthioethyimidazole)platinum(II)
Complex (vi) oxalato(2-methylthiomethylpyridine)platinum(II)
Complex (vii) oxalato(1-amino-2-thioethylpyridine)platinum (II)
Complex (viii) oxalato(1-amino-2-thiopropylpyridine)platinum (II)
Complex (ix) oxalato(1-amino-2-thiomethylethane)platinum(II)
Complex (x) oxalato(1-amino-2-thioethylethane)platinum(II)
Complex (xi) oxalato(2,5-dithiahexane)platinum(II)
Complex (xii) oxalato(2,5-diseleno hexane)platinum(II).

The above new complexes may be used in methods of treating cancer in patients, and in methods of manufacturing medicaments for treating cancer in patients

The complexes produced according to the method of the invention contain no traces of silver.

A second aspect of this invention is a method for producing a *bis*-oxalatoplatinate(II) salt which may be used in the method of the first aspect of the invention. The method according to the second aspect of the invention includes the step of either reacting a platinum(II) compound, such as K_2PtX_4 or reacting a platinum(IV) compound such as K_2PtX_6 where X is a halide such Cl, Br or I, preferably Cl, with an oxalate, wherein the platinum(II) or platinum(IV) compound and oxalate are reacted at a high mole ratio of greater than 1:4, preferably 1:8 or greater, more preferably 1:16 or greater most preferably 1:24 or greater.

In the case of the platinum(IV) compound, this compound is reduced to platinum(II) by the oxalate, or it may be reduced by another reducing agent such as SO_2 or sulfite.

The oxalate is typically $K_2C_2O_4$.

The platinum(II) *bis*-oxalato species is typically $K_2Pt(C_2O_4)_2.2H_2O$.

The platinum(II) compound or platinum(IV) compound and oxalate are typically reacted at a temperature of from 40°C to less than 100°C, preferably approximately 95°C, for a period of 0.5 to 4 hours, typically 1 hour.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph indicating the efficiency of the synthesis of $K_2Pt(C_2O_4)_2.2H_2O$ relative to the ratio of $K_2C_2O_4$ to K_2PtCl_6 in a reaction of K_2PtCl_6 with $K_2C_2O_4$ with a constant reaction time of 1h 15 min at 95°C;

Figure 2 is a graph indicating the time taken to reach an 85% yield of $K_2Pt(C_2O_4)_2.2H_2O$ relative to the oxalate to platinum ratio in the reaction of $K_2C_2O_4$ with K_2PtCl_6 at 95°C;

Figure 3 is a chromatographic analysis of the oxaliplatin product which did not dissolve when suspended in 6ml water, in Example 4;

Figure 4 is a chromatographic analysis of the oxaliplatin product of Figure 3 which has subsequently been washed with water, in Example 4; and

acts as a complexing agent and a light yellow precipitate starts to form. Thus the oxalate acts as a suitable complexing agent which can coordinate to the platinum to form $K_2Pt(C_2O_4)_2 \cdot 2H_2O$. Therefore, this method can be divided into two separate reactions. An alternative reducing agent such as SO_2 may be used in the place of the oxalate, to reduce the platinum IV to platinum II.

$$K_2PtCl_6 \xrightarrow[K_2C_2O_4]{} K_2Pt(C_2O_4)_2.2H_2O$$

In prior art methods which describe the synthesis of $K_2Pt(C_2O_4)_2.2H_2O$, a small excess of $K_2C_2O_4$ of up to 4 times was used at a temperature of 100°C for an extensive period (up to 18 hrs). See Shriver DF (Ed) 1979. Inorganic Synthesis, Vol. XIX: 16-17. During that time reduction of the platinum species occurs forming platinum metal (platinum black).

In accordance with an aspect of the method of this invention, the inventor has quite unexpectedly found out that when a platinum compound and oxalate are reacted at a high mole ratio of greater than 1:4, preferably greater than 1:8, more preferably greater than 1:16, most preferably 1:24 or greater and lower reaction temperatures (less than 100°C, typically 95°C), shorter reaction times are attained and no reduction to platinum metal (no platinum black) is observed. The higher concentration of the complexing anion, oxalate, not only acts as a stabilizater of the *bis*-oxalatoplatinate(II) species but also improves reaction rates as well as ligand exchange thus resulting in high yields of the *bis*-oxalatoplatinate(II) species. The larger the excess oxalate used, the higher the percentage yield of $K_2Pt(C_2O_4)_2.2H_2O$. (See Figure 1), when a 1:16 ratio of $K_2C_2O_4$ is used relative to K_2PtCl_6, the yield of $K_2Pt(C_2O_4)_2.2H_2O$ is only 67%. The yield consistently increases as the oxalate excess increases such that a ratio of 34:1 results in a 86% yield (See Figure 2). In Figure 2 the ratio of platinum to potassium oxalate is plotted against the time in minutes required to reach the maximum yield of the production of $K_2Pt(C_2O_4)_2.2H_2O$ from K_2PtCl_6, namely ~85%. Experiments performed with ratios of 8:1 or lower resulted

Step 3

The crude product may be purified by extracting the oxalatoplatinum(II) complex with sufficient excess of water. Contaminating $K_2Pt(C_2O_4)_2 \cdot 2H_2O$ which has similar solubility properties to the oxalatoplatinum(II) complex such as oxaliplatin at low temperatures may be removed by transforming it into $Cs_2Pt(C_2O_4)_2$ through addition of $Cs_2C_2O_4$ which upon cooling removes $Pt(C_2O_4)_2^{2-}$. The filtrate of this solution upon vacuum evaporation leaves a solid which can be washed with a small portion of hot water removing the residual amounts of $Pt(C_2O_4)_2^{2-}$ and oxalate salts. The white solid may be washed with cold water to obtain pure oxaliplatin. A further amount of oxalatoplatinum(II) complex may be obtained from the filtrate after removing $Cs_2Pt(C_2O_4)_2$ which precipitates after cooling. The final step consists of the recrystallization of the above white precipitate. A final oxaliplatin product has a chemical purity of >99.5% and optical purity of >99.98%. The overall yield of chemically and optically pure oxaliplatin is 15%.

Thus, the above method of the invention when used for producing oxaliplatin uses only 5 steps with an overall reaction time of 16 hours. It also requires the use of only four different chemicals, namely: K_2PtCl_6 / K_2PtCl_4, $K_2C_2O_4$, $Cs_2C_2O_4$ and a suitable neutral bidentate ligand.

The method described above may be used to form many other platinum(II) complexes with neutral bidentate ligands, and makes it possible to form platinum(II) complexes with neutral bidentate ligands that contain donor atoms other than N, typically S and Se, for example:

- neutral bidentate heterocyclic amines with an S donor atom, such as thioethereal S containing compounds of the general formula:

1-alkyl/aryl-2-alkylthioalkyl/aryl heterocyclic amines, particularly imidazoles or pyridines;

- aminoalkylthioalkyl/aryl compounds;
- dithioethers for example 2,5-dithiahexane;

Ligand (v)	1-butyl-2-methylthioethylimidazole,
Ligand (vi)	2-methylthiomethylpyridine,
Ligand (vii)	2-methylthioethylpyridine, or
Ligand (viii)	2-methylthiopropylpyridine.

17. The method according to claim 10, wherein the neutral bidentate ligand is an aminoalkylthioalkyl/aryl compound.

18. The method according to claim 17, wherein the neutral bidentate ligand is:

Ligand (ix)	1-amino-2-thiomethylethane, or
Ligand (x)	1-amino-2-thioethylethane.

19. The method according to claim 10, wherein the neutral bidentate ligand is a dithioether.

20. The method according to claim 19, wherein the neutral bidentate ligand is Ligand (xi) 2,5-dithiahexane.

21. The method according to claim 10, wherein the neutral bidentate ligand is a diseleno ether.

22. The method according to claim 21, wherein the neutral bidentate ligand is Ligand (xii) 2,5-diseleno hexane.

23. An oxalatoplatinum(II) complex containing a neutral bidentate ligand having a heterocyclic amine with a thioethereal S donor atom.

24. Oxalato(1-methyl-2-methylthioethylimidazole)platinum(II).

25. Oxalato(1-methyl-2-methylthiopropylimidazole)platinum(II).

26. Oxalato(1-butyl-2-methylthiomethylimidazole)platinum(II).

27. Oxalato(1-methyl-2-methylthiomethylimidazole)platinum(II).

28. Oxalato(1-butyl-2-methylthioethyimidazole)platinum(II).

29. Oxalato(2-methylthiomethylpyridine)platinum(II).

30. Oxalato(1-amino-2-thioethylpyridine)platinum (II).

31. Oxalato(1-amino-2-thiopropylpyridine)platinum (II).

32. Oxalato(1-amino-2-thiomethylethane)platinum(II).

33. Oxalato(1-amino-2-thioethylethane)platinum(II).

34. Oxalato(2,5-dithiahexane)platinum(II).

35. Oxalato(2,5-diseleno hexane)platinum(II).

36. A method of treating cancer in a patient, the method including administering an oxalatoplatinum(II) complex as defined in any one of claims 23 to 35 to the patient.

37. An oxalatoplatinum(II) complex as defined in any one of claims 23 to 35, for use in a method of treating cancer in a patient.

38. The use of an oxalatoplatinum(II) complex as defined in any one of claims 23 to 35 in a method of manufacturing a medicament for use in a method of treating cancer in a patient.

39. An oxalatoplatinum(II) complex product containing no traces of silver.

40. A method for producing a *bis*-oxalatoplatinate(II) species, the method including the step of either reacting a platinum(II) compound

or reacting a platinum(IV) compound with an oxalate at a high mole ratio of greater than 1:4.

41. The method according to claim 40, wherein the platinum(II) or platinum(IV) compound and oxalate are reacted at a high mole ratio of 1:8 or greater.

42. The method according to claim 41, wherein the platinum(II) or platinum(IV) compound and oxalate are reacted at a high mole ratio of 1:16 or greater.

43. The method according to claim 42, wherein the platinum(II) or platinum(IV) compound and oxalate are reacted at a high mole ratio of 1:24 or greater.

44. The method according to any one of claims 40 to 43, wherein the platinum(II) compound is K_2PtX_4 where X is a halide.

45. The method according to any one of claims 40 to 43, wherein the platinum(IV) compound is K_2PtX_6 where X is a halide.

46. The method according to claim 44 or 45, wherein X is Cl.

47. The method according to claim 45, wherein the platinum(IV) compound is reduced to platinum(II) by the oxalate.

48. The method according to claim 45, wherein the platinum(IV) compound is reduced by SO_2 or sulfite.

49. The method according to claim 40, wherein the oxalate is $K_2C_2O_4$.

50. The method according to claim 40, wherein the platinum(II) *bis*-oxalato species is $K_2Pt(C_2O_4)_2.2H_2O$.

51. The method according to any one of claims 40 to 50, wherein the platinum(II) compound or platinum(IV) compound and oxalate are reacted at a temperature of from 40°C to less than 100°C for a period of 0.5 to 4 hours.

52. The method according to claim 51, wherein the platinum(II) compound or platinum(IV) compound and oxalate are reacted at a temperature of approximately 95°C.

53. The method according to claim 51 or claim 52, wherein the platinum(II) compound or platinum(IV) compound are reacted for approximately 1 hour.